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Low dose quetiapine reverses deficits in contextual and cued fear conditioning in rats with excitotoxin-induced hippocampal neuropathy

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Abstract

Previous studies have demonstrated that adult rats with excitotoxic lesions of the hippocampus display deficits in memory-related behaviors similar to the memory deficits associated with schizophrenia. In this study, we assessed the sub-chronic effects of quetiapine, risperidone and haloperidol on performance deficits after intracerebroventricular administration of the excitotoxin, kainic acid, using paradigms for contextual and cued fear conditioning and spatial reversal learning in rats. The effects of three doses of quetiapine (5, 10 and 20 mg/kg) and single doses of risperidone (0.5 mg/kg) and haloperidol (0.15 mg/kg) were compared. Quetiapine administration at the lowest dose (5 mg/kg) reversed deficits in contextual and cued fear conditioning, but not deficits in spatial reversal learning, in kainic acid-treated animals. However, the two higher doses of quetiapine, and the single doses of risperidone and haloperidol, did not reverse any of the kainic acid-induced behavioral deficits. These results may be relevant to the effects of quetiapine and other antipsychotic drugs on memory deficits in patients with schizophrenia.

Keywords: Schizophrenia; Antipsychotics; Quetiapine; Memory; Hippocampus; Kainic acid

1. Introduction

Schizophrenia is characterized by deficits in memory, attention and executive control, as well as a variety of clinical phenomena, including psychosis, thought disorganization, and social withdrawal. Recently, efforts to ameliorate the cognitive deficits of schizophrenia have increased because of the relationship between these deficits and quality of life (Green, 1996; Alptekin et al., 2005; Milev et al., 2005). More specifically, memory impairments have been associated with poor vocational performance and a reduced capacity for forming and maintaining social relationships in patients with schizophrenia (Abi-Saab et al., 2005; Green et al., 2000).

We previously reported that the atypical antipsychotic drug, quetiapine, ameliorated memory deficits in subjects with schizophrenia, as compared to haloperidol, when they were switched to these treatments from a variety of other antipsychotic drugs (Velligan et al., 2002). In similar circumstances, risperidone has been reported to improve memory deficits in subjects with schizophrenia relative to haloperidol (Green et al., 1997). However, in subjects with schizophrenia, it is difficult to determine whether the apparent pro-cognitive effects of these drugs are primary, or secondary to decreases in neurological side-effects (e.g., pseudoparkinsonism and sedation) or improvements in other features of the illness (e.g., psychosis).

Animal models of experimentally induced cognitive deficits that are similar to the cognitive deficits observed in patients with schizophrenia may be useful for determining whether there are direct drug effects on specific aspects of cognition and the neurochemical systems related to them (Csernansky and Bardgett, 1998). In rats, intracerebroventricular (ICV) administration of the excitotoxin, kainic acid (KA) produces neuronal loss in the CA3 region of the hippocampus (Bardgett et al., 1995). The behavioral effects of ICV KA administration in rats include hyperactivity in response to novelty, dopamine agonists

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(e.g., amphetamine), and NMDA receptor antagonists (e.g., MK-801) (Bardgett et al., 1997a). In addition, ICV KA administration in rats produces deficits in auditory filtering (Stevens et al., 1998), prepulse inhibition of the acoustic startle response (Seybold et al., 1995), contextual (Stubley-Weatherly et al., 1996; Yin et al., 2002) and cued fear conditioning (Yin et al., 2002), and spatial memory (Handelmann and Olton, 1981). Several of these deficits, and particularly those related to memory, are analogous to cognitive deficits that have been observed in patients with schizophrenia (Csernansky and Bardgett, 1998).

The purpose of this study was to investigate the capacity of sub-chronic quetiapine to reverse memory-deficits in rats exposed to ICV KA administration. We compared the effects of quetiapine to risperidone, haloperidol, and saline and used spatial reversal learning and fear conditioning paradigms to assess memory performance. To examine the possibility that the drug treatments might also have non-specific behavioral effects, we also evaluated the animals' locomotion and shock sensitivity.

2. Materials and methods

2.1. Subjects

A total of 153 adult male Sprague–Dawley rats (2 months of age; 250–280 g; Harlan, Indianapolis, IN) was used in this study. The animals were randomly divided into 12 groups of 10–16 animals, based on availability of animals and survival after ICV KA administration (see below). The animals were housed on a 12:12 light/dark cycle, at constant temperature and humidity. Animals were housed 2–3 per cage, with food and water available ad libitum and handled daily for one week prior to experimentation. All animal procedures were consistent with the guidelines of the Animal Welfare Act, and were approved by the Animal Studies Committee of Washington University.

2.2. ICV KA or saline administration

KA was administered as described previously (Bardgett et al., 1995). Following administration of pentobarbital (60 mg/kg, i.p.), each animal was placed in a Kopf stereotaxic frame. The scalp was swabbed with betadine and a 2 cm incision made along the midline of the skull. Two small holes were drilled through the skull above each lateral ventricle, based upon the following coordinates with respect to bregma: −1.2 A/P, ±1.6 M/L. A 25-gauge needle attached to a 1 μl Hamilton syringe was slowly lowered 4.7 μ into the right ventricle. KA (3.8 nmol in 1 μl of saline) or saline (i.e., sham-lesioned) was then injected into the right lateral ventricle at a rate of 0.1 μl/2 min. Two minutes after the injection, the needle was slowly raised and the procedure was repeated for the left ventricle. Two minutes after the second injection, the needle was slowly raised and the skin was stapled together. Each animal was then placed in a heated recovery cage until fully awake. The animals were administered repeated doses of buprenorphine (0.5 mg/kg) 8 h apart as necessary for observed discomfort. Histological confirmation was not routinely used to check needle placement; however, the research assistant who performed the surgeries was trained using criteria that included histological confirmation of needle placement. If seizure activity was observed after surgery, diazepam (2–4 mg/kg) was administered IP. Animals were given 1–3 weeks to recover prior to behavioral testing.

2.3. Drug administration

After recovery from KA or saline administration, the animals were tested in two memory-related cognitive paradigms after being administered one of three doses of quetiapine, risperidone, haloperidol or saline (see below). Quetiapine (5, 10, and 20 mg/kg, Astra-Zeneca Pharmaceuticals, Delaware), risperidone (0.5 mg/kg, Janssen Pharmaceutica, New Jersey), haloperidol (0.15 mg/kg, Sigma, St. Louis, MO), or saline were injected subcutaneously (SC) into each animal one hour prior to behavioral testing on 4 consecutive days for T-maze adaptation and testing, followed by a three day drug holiday without drug injections or behavioral testing. Then, the animals were injected again (SC) for five additional consecutive days, one hour prior to testing for locomotion and fear conditioning.

Animals were assigned to a single drug and drug dose throughout the experiment. The drug doses were selected based on our previous studies of the effects of antipsychotic drugs in KA-lesioned rats (Bardgett et al., 1997b, 2002; Csernansky et al., 2001), and the available literature on the effects of typical and atypical antipsychotic drug on behaviors in rats that are predictive of antipsychotic effects and motor side-effects in subjects with schizophrenia (Arnt, 1995; Goldstein, 1996). Drugs were prepared at concentrations such that each animal received a constant volume of 1 ml/kg body weight.

2.4. Behavioral assessment

2.4.1. Spatial reversal learning

For three days prior to behavioral testing, animals were housed singly and given a restrict amount of food, so that they were maintained at or slightly above 90% of their non-restricted body weight.

T-maze testing was conducted in a clear Plexiglas maze. Each animal was adapted to the maze once daily during the food deprivation period. On each adaptation day, 10 Honey Nut Cheerios were scattered randomly throughout the maze. Animals were individually placed in the T-maze for ten minutes during three adaptation sessions. On day 4, a single Cheerio was placed in a randomly assigned "choice arm"; the animal was then placed in the start box, and the first arm entry was recorded. The animal was then removed, the same "choice arm" was baited, and the animal was again placed in the start box. This continued until the animal made the correct choice in 8 of 10 trials. Immediately following acquisition of the task, to assess reversal learning, a single Cheerio was placed in the "opposite arm", and again the

animal was placed in the start box, and a series of trials were run until the animal made the correct choice in 8 of 10 trials.

2.4.2. Locomotor activity

Three days after T-maze testing, each animal was placed in an empty cage for 60 min to assess spontaneous locomotion. The animals were tested individually in clear Plexiglas cages (46 cm long × 25.5 cm wide × 21.5 cm high) equipped with 12 photobeams spaced 5 cm apart. These photoelectric sensors were connected to a computer that tabulated the total number of breaks in the photobeam.

2.4.3. Fear conditioning

One day after locomotion testing, fear conditioning was tested using methods described previously (Yin et al., 2002). Five days after completion of T-maze testing, animals were trained and tested in one of two Plexiglas conditioning chambers (model ENV-108, Med-Associates, St. Albans, VT) each measuring 30 cm wide, 25 cm high, and 24 cm long and containing a metal grid floor. Each chamber was housed within a larger sound-attenuating chamber containing a fan that provided 70 dB background noise, a white light, and a viewing window to observe the animals.

During training, the conditioning chamber contained a piece of absorbent cotton soaked in mint extract and placed in a cup below the grid floor of the conditioning chamber. Three minutes after being placed in the conditioning chamber, an 80 dB, 2800 Hz tone was presented for 20 s. During the last one second of the tone, the animals also received a 0.1 mA continuous foot shock. This pairing was repeated every minute for the next two minutes. The animals were removed from the testing cage 40 s after the third shock. Throughout the entire 5-min conditioning chamber exposure, the presence or absence of freezing behavior, defined as no movement other than normal respiratory movements, was recorded every 10 s.

One day later, each animal was placed in the conditioning chamber to test for the presence of freezing behavior in response to the context. The chamber was unaltered and again contained a mint scented cotton ball. The animals were observed for 8 min in the unaltered context and freezing behavior recorded every 10 s. On the third day of fear conditioning, the chamber was partially altered by covering the grid floor with a sheet of smooth polyurethane, and drops of coconut extract were placed on a cotton ball in a mesh-covered cup inside the chamber. The light was on during the entire 10 min testing period, but the tone was presented only during the last 8 min of testing. The presence or absence of freezing behavior was recorded every 10 s during the tone-free first two minutes of the test (i.e., freezing behavior in response to an altered context), and then every ten seconds during presentation of the tone (i.e., freezing behavior in response to a cue).

2.4.4. Shock sensitivity

To determine whether the experimental conditions altered the animals' sensitivity to the shock used in the fear conditioning paradigm, shock sensitivity was tested 24 h after paradigm completion. Animals were placed in a conditioning chamber for 2 min and then exposed to 2 s shocks of increasing intensity (shocks started at 0.05 mA and were increased by 0.05 after each interval) every 20–30 s. The level of shock (in mA) required to evoke jumping was determined.

2.5. Data analysis

As a measure of the capacity for reversal learning, the number of trials required to achieve a predetermined criterion (8 of 10 correct trials) was used. As a measure of the capacity for contextual or cued memory, the percentage of time spent freezing during each trial type (context, cued and altered context) was used.

F-tests were used to evaluate whether variances between groups were equal. Variances were significantly different between KA-lesioned and sham-lesioned animals for the data collected during contextual and cued fear conditioning. This precluded using two-way ANOVA to evaluate the primary effects of drug and lesion status and the interaction between them. Alternatively, to assess the effects of lesion status on behavior, we used Mann–Whitney *U* tests. Kruskal–Wallis tests were then run separately in KA-lesioned and sham-lesioned animals to determine the effects of the various drug conditions. Post hoc comparisons between drug groups were made using Mann–Whitney U tests.

3. Results

3.1. Spatial reversal learning and locomotor activity

There were no overall effects of lesion status (Mann–Whitney U, $z=-0.29$, $p=0.77$) or drug condition (Kruskal–Wallis, $H=6.36$, $p=0.27$) on acquisition of the T-maze task. There was the expected overall effect of lesion status on reversal learning (Mann–Whitney U, $z=-2.86$, $p<.01$) (see Fig. 1). However, there was no overall effect of drug condition on reversal learning (Kruskal–Wallis, $H=6.26$, $p=0.28$). To examine whether the drug conditions may have altered locomotor activity, which in turn interfered with the evaluation of the effect of drug condition on reversal learning, we examined the effects of drug condition on locomotor activity. There was an overall effect of drug condition (Kruskal–Wallis, $H=82.73$, $p<0.0001$), but not of lesion status (Mann–Whitney, $z=-0.58$, $p=0.56$), on locomotor activity. Post hoc Mann–Whitney U tests showed that there was a significant decrease in locomotor activity in KA-lesioned (Mann–Whitney U, $z=-4.74$, $p<0.0001$) and sham-lesioned (Mann–Whitney U, $z=-4.45$, $p<0.0001$) animals that had received haloperidol as compared to saline-injected animals. Also, in sham-lesioned animals only, animals administered risperidone showed a significant decrease in locomotor activity (Mann–Whitney U, $z=-3.44$, $p=0.0006$) as compared to saline controls (see Fig. 2). Quetiapine, at the highest dose, increased locomotor activity in both KA-lesioned (Mann–Whitney U, $z=-2.44$, $p=0.01$) and sham-lesioned (Mann–Whitney U, $z=-2.01$, $p=0.04$) animals, as compared to saline controls.

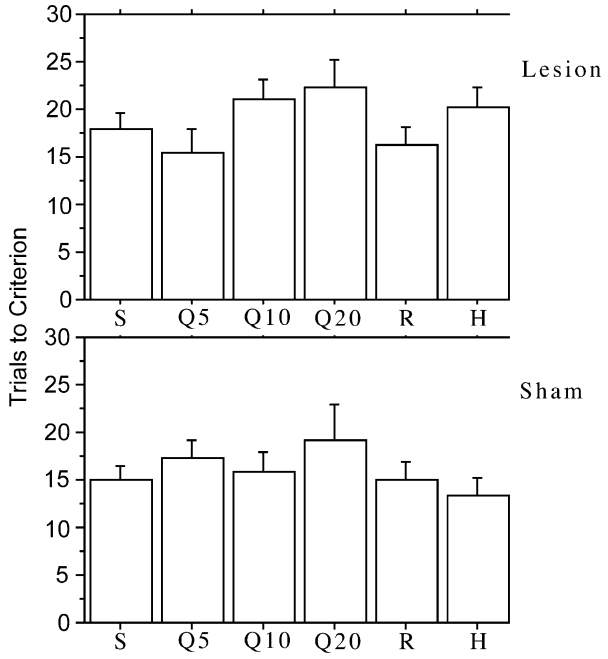

Fig. 1. Spatial reversal learning in rats following ICV KA or saline administration. The effect of lesion status on trials to criterion during reversal learning was significant. However, the effect of drug condition on trials to criterion was not significant (see text for statistics). Abbreviations: saline=S; quetiapine 5 mg/kg=Q5; quetiapine 10 mg/kg=Q10; quetiapine 20 mg/kg=Q2; risperidone 0.5 mg/kg=R; haloperidol 0.15 mg/kg=H.

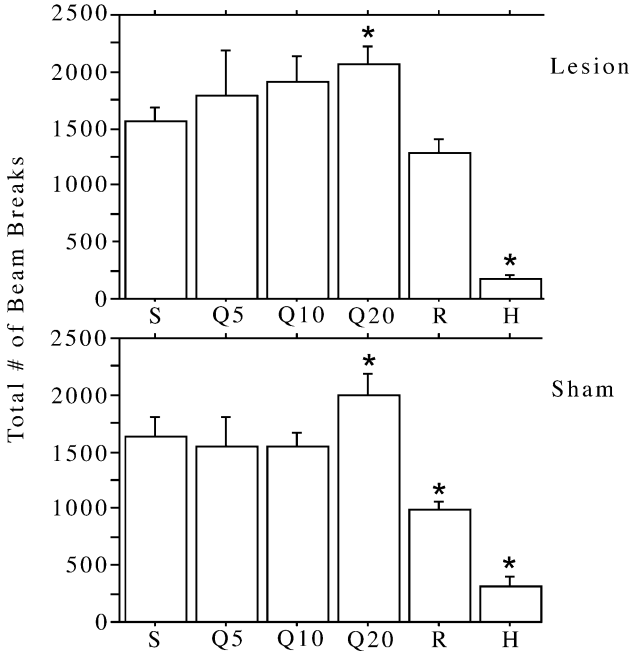

Fig. 2. Locomotor activity in rats following ICV KA or saline administration. There was a significant effect of drug treatment but not lesion status on total number of beam breaks in one hour (see text for statistics). Mann–Whitney *U* testing revealed a significant decrease in beam breaks in both sham-lesioned and KA-lesioned rats administered haloperidol as compared to saline controls, a decrease in beam breaks in sham-lesioned rats administered risperidone as compared to saline controls, and an increase in beam breaks in sham-lesioned and KA-lesioned animals administered 20 mg/kg quetiapine (indicated by *). Refer to Fig. 1 legend for abbreviations.

No other significant between-group differences in locomotor activity were seen.

3.2. Fear conditioning and shock sensitivity

The overall effect of lesion status on training for the fear conditioning paradigm was significant (Mann–Whitney *U*, $z=2.00$, $p=.046$); also, the overall effect of drug condition on training for the fear conditioning paradigm was significant (Kruskall–Wallis, $H=46.28$, $p<0.0001$). In post hoc testing, the effect of drug condition on training for the fear conditioning paradigm was significant in KA-lesioned animals (Kruskal–Wallis, $H=26.39$, $p<0.0001$). Post hoc Mann–Whitney *U* testing revealed a significant increase in freezing during training in KA-lesioned animals that had received the 5 mg/kg (Mann–Whitney *U*, $z=2.91$, $p=0.004$) and 10 mg/kg (Mann–Whitney *U*, $z=3.33$, $p=0.0009$) doses of quetiapine as compared to saline. There was also a significant effect of drug condition on training in sham-lesioned animals (Kruskal–Wallis, $H=27.61$, $p<0.0001$). Post hoc Mann–Whitney *U* tests again showed a significant increase in freezing during training at the 5 mg/kg (Mann–Whitney *U*, $z=2.39$, $p=0.02$), the 10 mg/kg (Mann–Whitney *U*, $z=3.52$, $p=0.0004$), and 20 mg/kg (Mann–Whitney *U*, $z=2.69$, $p=0.007$) doses of quetiapine as compared to saline.

There was a significant overall effect of lesion status on contextual fear conditioning (Mann–Whitney *U*, $z=2.61$, $p<0.01$) and cued fear conditioning (Mann–Whitney *U*,

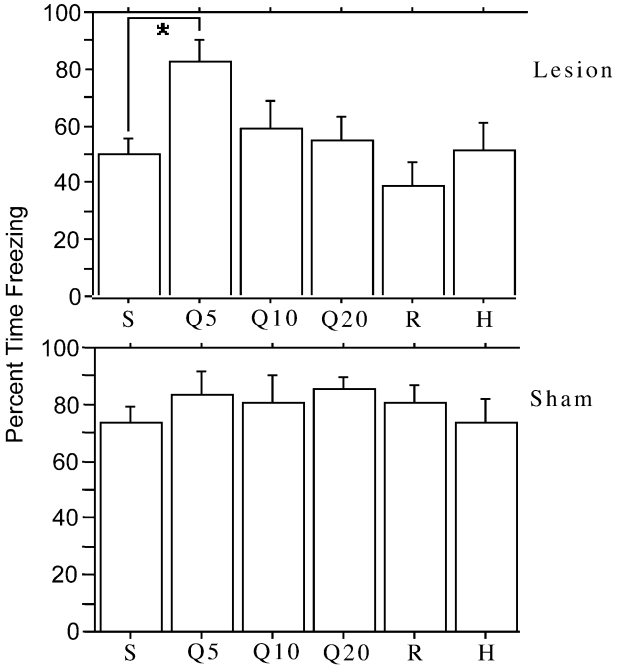

Fig. 3. Contextual fear conditioning in rats following ICV KA or saline administration. The effect of lesion status on percent time freezing was significant. The effect of drug condition in KA-lesioned animals was significant. Mann–Whitney *U* testing revealed a statistically significant difference in KA-lesioned animals administered quetiapine 5 mg/kg and saline (indicated by *). There was no effect of drug condition on sham-lesioned controls (see text for statistics). Refer to Fig. 1 legend for abbreviations.

$z=2.49$, $p=0.01$) (see Figs. 3 and 4). However, there was also a significant effect of lesion status on altered context conditioning (Mann–Whitney U, $z=2.31$, $p=0.02$). The overall effects of drug condition on contextual fear conditioning (Kruskal–Wallis, $H=8.96$, $p=0.11$) and cued fear conditioning (Kruskal–Wallis, $H=9.45$, $p=0.09$) were not significant. However, in post hoc testing, a significant effect of drug condition was observed in KA-lesioned animals during contextual fear conditioning (Kruskal–Wallis, $H=11.87$, $p=0.04$ (see Fig. 3)). Post hoc Mann–Whitney U testing revealed a significant increase in freezing during contextual fear conditioning in KA-lesioned animals treated with the lowest dose of quetiapine (5 mg/kg) as compared to saline-treated animals (Mann–Whitney U, $z=3.05$, $p=0.002$). No other significant differences were observed between individual drug conditions as compared to saline during contextual fear conditioning. Also, there was no significant effect of drug condition on altered context conditioning in KA-lesioned animals (Kruskal–Wallis, $H=2.78$, $p=0.73$). Finally, in sham-lesioned animals, there was no significant effect of drug condition on contextual fear conditioning (Kruskal–Wallis, $H=2.82$, $p=0.73$), nor on altered context conditioning (Kruskal–Wallis, $H=9.30$, $p=0.10$). A trend towards a significant drug effect on cued fear conditioning was observed in KA-lesioned animals (Kruskal–Wallis test, $H=10.08$, $p=0.07$) (see Fig. 4). Post hoc Mann–Whitney U tests revealed an increase in freezing behavior in animals treated only with the lowest dose of quetiapine (5 mg/kg) as compared to saline controls (Mann–Whitney U, $z=2.86$, $p=0.004$). In sham-lesioned animals, there was no effect of drug condition on cued fear conditioning (Kruskal–Wallis, $H=3.28$, $p=0.65$).

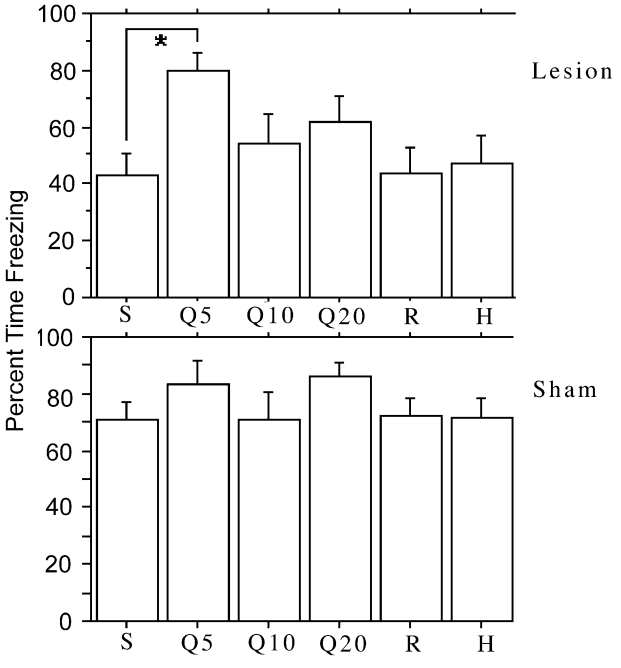

Fig. 4. Cued fear conditioning in rats following ICV KA or saline administration. The effect of lesion status on percent time freezing was significant. The effect of drug condition in KA-lesioned animals only trended towards significance. Mann–Whitney U testing revealed a significant increase in freezing in rats administered 5 mg/kg quetiapine compared to saline-injected KA-lesioned controls (indicated by *). There was no effect of drug condition on sham-lesioned controls (see text for statistics). Refer to Fig. 1 legend for abbreviations.

There was no overall effect of lesion status (Mann–Whitney U, $z=0.06$, $p=0.95$), nor of drug condition (Kruskall Wallis, $H=4.17$, $p=0.52$), on shock sensitivity. Further, in KA-lesioned animals, there was no significant effect of drug treatment on shock sensitivity (Kruskal–Wallis, $H=4.20$, $p=0.52$). There was also no significant effect of drug condition (Kruskal–Wallis, $H=6.23$, $p=0.29$) in sham-lesioned animals.

4. Discussion

As expected, we found impairments in contextual and cued fear conditioning and reversal learning in rats that had been administered ICV KA. We have reported previously that KA administered in this way produces prominent neuronal loss in the hippocampus, especially in the CA3 subfield (Bardgett et al., 1995). The lowest dose of quetiapine tested was effective in ameliorating deficits in contextual fear conditioning, and a similar trend was observed for cued fear conditioning. However, quetiapine failed to ameliorate ICV KA-induced deficits in reversal learning. At the single dose tested, risperidone failed to ameliorate the behavioral deficits produced by ICV KA administration. In turn, haloperidol also failed to ameliorate KA-induced deficits in contextual and cued conditioning and in reversal learning, and even decreased freezing during the training period for the fear conditioning paradigm. Improvement on these tasks was not seen with any drug treatment in sham animals, possibly due to a ceiling effect. The results of this study suggest subchronic administration of quetiapine, at least at one dose, has direct beneficial effects on memory in rats with KA-induced hippocampal neuropathy, and support the hypothesis that its precognitive effects in patients with schizophrenia (Velligan et al., 2002) may be primary rather than secondary to its differential efficacy or neurological side-effect profile as compared to conventional antipsychotic drugs.

Although we did not expect haloperidol to reverse the behavioral deficits induced by ICV KA administration, we were surprised that the single dose of risperidone used in this study (0.5 mg/kg) had no pro-cognitive effects in our animal model. We had previously observed this dose of risperidone to reverse memory deficits in KA-lesioned rats (Csernansky et al., 2001) and clinical studies suggest that risperidone as compared to haloperidol also has cognitive-enhancing effects in schizophrenia patients. A small, but statistically insignificant, beneficial effect of risperidone was observed in the reversal learning paradigm, which is in keeping with our prior results (Csernansky et al., 2001). However, risperidone as well as haloperidol decreased locomotor activity and this non-specific behavioral effect may have confounded performance on the T-maze test. Alternatively, the results of the present study may suggest that risperidone exerts its pro-cognitive via a different mechanism than quetiapine, and one that is not

represented by the KA-lesion model. Finally, risperidone may have had pro-cognitive effects in our model had we used different doses or longer periods of drug administration. While recent work suggests that the antipsychotic effects of such drugs can be seen within several days (Agid et al., 2003; Kapur et al., 2005), manifestation of the pro-cognitive effects of such drugs in schizophrenia patients usually required longer periods of time.

Our results suggest that the lowest dose of quetiapine was superior to the two higher doses of quetiapine in reversing cognitive deficits induced by ICV KA administration. This was also somewhat surprising, since studies of the clinical and cognitive effects of quetiapine in patients with schizophrenia found higher doses (i.e., 600 mg/day) to be superior to lower doses (i.e., 300 mg/day) (Small et al., 1997; Velligan et al., 2002). The explanation for this discrepancy may simply lie in the difficulty of defining equivalent doses of any drug in rodents and in human beings. Kapur et al. (2003) reported that the dose of quetiapine required to reach 65–80% D2 receptor occupancy in adult Sprague–Dawley rats (i.e., a minimum dose required to achieve antipsychotic effects) was 10–20 mg/kg, and our most effective dose of quetiapine was below this range. Finally, it should be noted that repeated administration of quetiapine, risperidone and haloperidol for several days could have induced tolerance and/or sensitization to the effects of these drugs (Csernansky et al., 1990). Resolution of this last issue will require additional studies where the dosing intervals as well as the daily dose of the test drugs are systematically varied.

The results of this study give support to the general hypothesis that atypical antipsychotic drugs can have primary cognition-enhancing effects in an animal model of excitotoxin-induced hippocampal neuropathy. Hopefully, these results are of significance to patients with schizophrenia, since hippocampal neuropathy has been observed as a feature of the illness (Csernansky et al., 2002). Also, hippocampal neuropathy is a critical feature of Alzheimer's disease (Arnold et al., 1991), and atypical antipsychotic drugs are often used to treat the behavioral agitation associated with this degenerative brain disease. Thus, further investigation of the behavioral effects of quetiapine and other antipsychotic drugs in animal models of experimentally induced cognitive deficits may be helpful in the development and refinement of drug treatment for a wider variety of neuropsychiatric disorders.

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